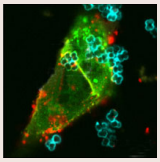
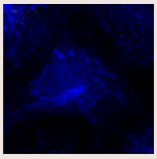
In this issue

By Jane Bradbury



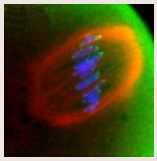
Caveolin-1 and pathogen uptake

Pathogenic bacteria use various endocytic pathways and receptors to enter eukaryotic host cells. Among the receptors highjacked for pathogen uptake are integrins – glycoproteins involved in cell adhesion, migration and proliferation. Integrins also mediate endoctyosis and, on p. 4280, Christof Hauck and colleagues provide new insights into the integrin-mediated uptake of *Staphylococcus aureus*, a leading cause of hospital-acquired infections, into mammalian cells. The authors report that integrin binding by fibronectin-coated bacteria triggers the redistribution of several membrane microdomain-associated components, including gangliosides, GPI-linked proteins and caveolin-1. They show that disruption of membrane-microdomains blocks bacterial internalisation, whereas – surprisingly – genetic deletion or siRNA-mediated knockdown of caveolin-1 enhances this process. Moreover, the mobility of membrane microdomains is increased in caveolin-1-deficient cells, and both this enhanced mobility and increased bacterial internalisation are repressed by re-introduction of wild-type caveolin-1, but not by a caveolin-1 scaffolding-domain mutant. Together, these results identify a role for caveolin-1 in reducing membrane microdomain mobility that affects bacterial internalisation and that might also influence integrin turnover at focal adhesion sites.



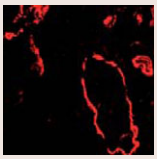
Tapping into antigen presentation

The presentation of intracellular peptides to cytotoxic T cells by major histocompatibility complex (MHC) class I molecules is an important part of the body's immune defence mechanism. Cytotoxic T cells ignore cells that present self-peptides but kill virus-infected cells that present foreign peptides. Crucially, the transporter associated with antigen processing (TAP) protein translocates cytosolic peptides into the endoplasmic reticulum (ER) lumen for antigen presentation. TAP function in the ER has been extensively studied, but is TAP also active in post-ER compartments? Sebastian Springer and colleagues now report that the answer to this question is yes (p. 4271). Using fluorescence microscopy, the authors show that TAP is present in the ER–Golgi intermediate compartment and in the Golgi complex in fibroblasts and lymphocytes, and they detect its activity in these compartments using a fluorescently labelled peptide probe. Then, using an in-vitro vesicle formation assay, they show that COPII vesicles, which carry secretory cargo out of the ER, contain TAP that is associated with MHC class I molecules. Thus, suggest the authors, peptide translocation by TAP and peptide loading onto class I molecules is not confined to the ER, but can occur throughout the early secretory pathway.



A meiotic tale of two Auroras

The chromosome passenger complex (CPC), which contains the serine/threonine kinase Aurora B, the inner centromere protein ICENP, survivin and borealin, regulates chromosome segregation and cytokinesis during mitosis. Less is known about CPC's role in female meiosis, partly because mammalian oocytes contain two CPC forms: an Aurora-B- and an Aurora-C-containing form. Now, David Glover, Magdalena Zernicka-Goetz and colleagues (p. 4292) reveal that CPC is required for faithful chromosome transmission and cytokinesis during mouse oocyte maturation. They show that depletion of INCENP or combined inhibition of Aurora B and C leads to the activation of the anaphase-promoting complex or cyclosome (APC/C) before the chromosomes have correctly aligned, and then subsequently prevents cytokinesis. Importantly, however, whereas overexpression of Aurora C has a dominant-negative effect on the CPC, advances APC/C activation and prevents cytokinesis, overexpression of Aurora B prevents APC/C activation, stabilises securin and leads to failure of homologous chromosomes to separate in meiosis I. Thus, the authors conclude, Aurora B and Aurora C have overlapping, but partly independent, roles in mammalian meiosis.



CEACAM1 regulates vessel permeability

Carcinoembryonic antigen cell adhesion molecule-1 (CEACAM1) is an immunoglobulin-like co-receptor that is expressed on epithelial, haematopoietic and endothelial cells. CEACAM1 is involved in the regulation of vascular remodelling, but does it have any role in angiogenesis (the formation of new blood vessels from a pre-existing vascular bed)? On page 4221, Nicole Beauchemin and colleagues report that CEACAM1 is a key regulator of vascular endothelial growth factor receptor-2 (VEGFR2)-mediated angiogenesis and vascular permeability in vitro and in vivo. To assess the global impact of CEACAM1 on angiogenesis, the authors investigate the consequences of CEACAM1 deletion in endothelial cells. They report that basal vascular permeability in several tissues and in tumours is increased in *Ceacam1*$^{-/-}$ mice because of ultrastructural damage to blood vessels. This phenomenon, they show, correlates with increased basal activation of Akt (a serine/threonine kinase) and endothelial nitric oxide synthase (eNOS), and with reduced VEGF-induced nitric oxide production in primary mouse lung endothelial cells. Moreover, CEACAM1 is phosphorylated upon treating the cells with VEGF. These and other data reveal a functional link between CEACAM1 and the VEGFR2–Akt–eNOS-mediated pathway that controls vascular permeability and angiogenesis.

SIRT2 regulation of NF-κB activity

The nuclear factor κB (NF-κB) family of inducible transcription factors regulates the expression of a large number of target genes involved in immune and inflammatory responses, apoptosis and cell proliferation, differentiation and survival. Previous studies have shown that acetylation of p65, one of the five mammalian NF-κB family members, has an important role in the regulation of NF-κB-dependent transcription. Now, Michael Hottiger and colleagues (p. 4251) characterise SIRT2, a member of the sirtuin family of NAD^+-dependent histone deacetylases, as a p65 deacetylase. The authors show that SIRT2 interacts with p65 in the cytoplasm of mouse embryonic fibroblasts, and deacetylates p65 in vitro and in vivo at Lys310. They report that p65 is hyperacetylated at this residue in *Sirt2*$^{-/-}$ cells after stimulation with TNFα, a proinflammatory cytokine that induces NF-κB activation and nuclear translocation. Importantly, hyperacetylation of p65 in *Sirt2*$^{-/-}$ cells results in an increase in the expression of a subset of p65 acetylation-dependent target genes. On the basis of these and other results, the authors propose that deacetylation of p65 by SIRT2 in the cytoplasm is an important regulator of TNFα-induced NF-κB-dependent gene expression.

Development in press

Pak1-ing a punch in lumen formation

The generation and maintenance of correct lumen size and shape is essential for the function of tubular organs. In *Development*, Monn Monn Myat and co-workers report that p21-activated kinase (Pak1) has a novel role during lumen formation in *Drosophila* embryonic salivary glands. The researchers show that Pak1 regulates the size and elongation of the apical domain of individual epithelial cells in the developing gland by decreasing and increasing E-cadherin levels at adherens junctions and basolateral membranes, respectively. Pak mediates these effects, they report, through Rab5- and dynamin-dependent endocytosis of E-cadherin. Moreover, constitutively active Pak1 induces the formation of multiple intercellular lumens in the gland, an effect that is dependent on Rab5 and dynamin, and on the Pak1 substrate Merlin. Together, these results identify a crucial role for Pak1 and E-cadherin endocytosis in lumen size and shape determination in fly salivary glands, and highlight a mechanism for multiple lumen formation – a process that occurs in pathological conditions such as breast ductal carcinoma in situ.

Pirraglia, C., Walters, J. and Myat, M. M. (2010). Pak1 control of E-cadherin endocytosis regulates salivary gland lumen size and shape. *Development* **137**, 4177-4189.